REMARKS

Pursuant to this amendment, claims 1-16 are pending in the application, with claims 10-12 being withdrawn from consideration, subject to an election of species. In particular, to expedite prosecution, Applicants have amended 1, 9, 13, 15, and 16 as follows:

Claims 1 and 9 have been amended to refer to a method of screening for early cancer rather than a method for detecting early cancer. Support for this amendment is found in the specification as originally filed, particularly at p. 2, line 35 – p. 3, line 6; p. 5, line 29 – p. 6, line 1; p. 7, lines 19 – 24; p. 19, lines 18 – 19; and p. 20, lines 8 – 10. As noted in the specification, screening targets a broad range of symptomless subjects to find patients affected by a particular disease. In contrast to detection, the detection of cancer targeting a particular subject is called diagnosis, whereas screening targets arbitrary groups. In the present invention, screening and diagnosis differ only in their targets, and the cancer detection method of the present invention comprises both.

Claims 1 and 9 have further been amended to define "early cancer" as cancer at stage 0 or stage I of the TNM classification. Support for this amendment is found in the specification as originally filed, particularly at p. 4, lines 16 – 28. Appendix 1 is submitted herewith to further explain the TNM classification system and what parameters correspond to stage 0 and stage I.

Claims 1, 9, and 13 have been amended to clarify that the midkine protein at issue is "human midkine in a body fluid". Support for these amendments can be found throughout the specification as originally filed, including, for example page 3, line 1 to page 3, line 4.

Claim 13 has been amended to refer to "tumor treatment". Support for this amendment is found in the specification as originally filed, particularly at p. 9, lines 1 – 7.

The phrase "one step" has been canceled from claims 15 and 16. Claims 15 and 16 have been further amended for antecedent basis purposes.

In sum, Applicants respectfully submit that no new matter has been added.

Rejections under 35 U.S.C. 112, First Paragraph (New Matter)

In the outstanding final office action, the Examiner rejects claims 13-16 under 35 U.S.C. § 112, first paragraph, as containing subject matter not described in the specification in such a way as to convey possession of the claimed invention (i.e., a new matter rejection). Specifically, the Examiner finds the recitations "before and after treatment using a one-step sandwich enzyme immunoassay", "comparing the level measured after treatment to a level measured before treatment", and "wherein a reduction. . .after treatment is indicative of successful therapy and positive prognosis" are not supported by the originally filed specification.

At the outset, it is important to note that satisfaction of the written description requirement does not require in *haec verba* antecedence in the originally filed application. Rather, the inquiry is whether one following applicant's specification would necessarily select the later claimed subject matter. The question, therefore, is whether the originally filed application would have conveyed to a person of ordinary skill in the art that applicants invented the subject matter later claimed by them including the limitations in question.

In this case, the originally filed specification repeatedly refers to "assessing cancer prognosis". See p. 4, lines 5-9 and original claim 13 (p. 22). The specification further states that the tumor markers find utility in "monitoring the course of treatment". See p. 20, lines 8-10. Finally, in the paragraph beginning at p. 8, line 29, and extending to p. 9, line 7, the specification states "MK is useful not only for diagnosis of cancer, but also as an indicator for monitoring the course of the disease, as a prognostic factor, or for monitoring relapse. . . .if a decrease in the MK value is measured before and after tumor treatment, and a decrease in the value is confirmed, one can speculate that the treatment being performed is effective. Furthermore, if the measured MK value decreases to that of a healthy subject, one can speculate that tumor treatment has been successful." Thus, it is readily apparent that the steps of measuring and comparing MK levels before and after tumor treatment and correlating reduction with successful therapy and positive prognosis finds support in the specification as originally filed. Accordingly, Applicants respectfully submit that the new matter rejection is in error and should be withdrawn.

Rejections under 35 U.S.C. 112, First Paragraph (Written Description)

The Examiner further rejects claims 1-9 and 13-16 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner has rejected claims 1-9 and 13-16 under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. Specifically, the Examiner finds the recitations of "human midkine protein" and "human midkine protein that lacks a domain near the N-terminus" to encompass a genus of proteins because "Applicants have not provided sufficient evidence clearly demonstrating that there is only one known human midkine sequence. . .with an amino acid sequence known in the art" nor do they "explicitly detail what amino acid residues are lacking from [the N-terminus of] the sequence."

To expedite prosecution, Applicants have deleted reference to a human midkine protein that lacks a domain near the N-terminus. In any event, the issue is not whether the instant claims encompass a "genus" of proteins but whether there is *substantial variation* within the genus such that a variety of representative species are needed to reflect the variation. In fact, the published guidelines for examination of the "written description" requirement of 35 U.S.C. §112, first paragraph explicitly state that "a single species may, in some instances, provide an adequate written description of a generic claim when the description of the species would evidence to one of ordinary skill in the art that the invention includes the genus". See FR Vol. 66, No. 4 (2001), p, 1102 - comment (16). Moreover, the training materials with respect to written description guidelines clearly suggest that the Examiner has the initial burden of showing that the species encompassed by the claimed genus are expected to be widely divergent and highly variable in terms of structure and the like. See, for example, Example 17.

Possession of a genus may be satisfied through sufficient description of a "representative number of species" by (a) actual reduction to practice, (b) reduction to drawings, or (c) by disclosure of *relevant, identifying characteristics*, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlation between function and structure. A "representative number of species" means that the species that are actually described are representative of the entire genus. Thus, when there is substantial

variation within the genus, one must describe a sufficient variety of species to reflect the variation; conversely, when there is little or no variation in the genus, a single species will suffice.

The Examiner makes much of the fact that Applicants have not provided sufficient evidence clearly demonstrating that there is only "one known human midkine sequence". However, as noted above, the issue is not whether only one sequence exists but whether substantial variation exists among proteins known in the art as human midkine. In the instant case, human midkine is a well characterized protein whose structure and function are well known in the art. Specifically, as discussed in the specification, human midkine is a retinoic acid-responsive gene product and heparin-binding growth/differentiation factor, a 13-kDa polypeptide rich in basic amino acids and cysteines having nucleotide and amino acid sequences as set forth in USPN 5,461,029, the contents of which are incorporated by reference in the instant specification (see p. 5, lines 4-6, and p. 11, lines 29-30). Furthermore, when searching the NCBI's protein database for human midkine, one finds four sequence submissions directed to Midkine [*homo sapiens*], each of which describe an identical 143 amino acid residue protein. See specifically NP002382 (GI: 4505135), AAH11704 (GI: 15079798), BAA0147 (GI: 219929), and AAA58478 (GI:182651). Accordingly, if the "genus" of "human midkine" is indeed a genus at all, it clearly does not permit substantial variation. Furthermore, since Applicants' specification clearly sets forth the distinguishing identifying characteristics needed to identify members of the "genus", the limited species disclosed are sufficient to demonstrate possession thereof.

The Examiner further notes that the definition of midkine in the specification mentions fragments and mutants. However, these embodiments have clearly been excluded through prior claim amendments. Nevertheless, to further clarify this point and expedite prosecution, the instant claims have been amended to refer to "human midkine in a body fluid". Contrary to the Examiner's suggestion, not all midkine fragments and mutants are found in a body fluid. In fact, Applicants have described only two embodiments of human midkine that are secreted into body fluid and expressed cancer specifically – full-length, wild-type human midkine and human

midkine lacking an N-terminus domain. Both forms of human midkine are well-known in the art. The former is discussed above. The latter is not only described by Kaname et al. in Biochem. Biophys. Res. Commun., 219: 256-260, 1996, the contents of which are incorporated by reference herein, and the instant specification at page 5, lines 2-5, but it is also mentioned in the Song reference cited by the Examiner (see p. 379, col. 2 as well as reference numbers 18 and 19). Accordingly, if the claimed "human midkine in body fluid" indeed constitutes a genus, it is clearly not widely variable. Furthermore, since Applicants have clearly set forth the distinguishing identifying characteristics needed to identify members of the "genus", the limited species disclosed are sufficient to demonstrate possession thereof.

In sum, Applicants respectfully submit that the originally filed specification provides sufficient written description of the invention of the pending claims so as to demonstrate possession thereof. Accordingly, Applicants request that the written description rejection be reconsidered and withdrawn.

Rejections under 35 U.S.C. 112, First Paragraph (Enablement)

The Examiner further rejects claims 1-9 and 13-16 under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a methods involving the step of measuring the level of human midkine protein in a biological sample, does not reasonably provide enablement for methods involving measuring the level of a midkine mutant or midkine fragment.

The Examiner states that Applicants' experimental evidence demonstrates the utility of full-length human midkine but not "mutants and arbitrary fragments of MK." See p. 8, lines 8-10. However, as noted above, the instant claims do not encompass "arbitrary" mutants or fragments of "MK". Rather, the claims are narrowly tailored to "human midkine in a body fluid". Applicants and other researchers have clearly demonstrated that human midkine secreted into a body fluid is expressed in a cancer specific manner such it may readily be used in the detection of early cancer and the assessment of cancer prognosis as claimed. See, for example, the Test Examples 1-9 of the instant specification (pages 15-21) as well as Kaname T. et al.:

Biochem. Biophys. Res. Commun., 219: 256-260, 1996. Accordingly, one skilled in the art could readily perform the methods of the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

Thus, Applicants respectfully submit that the scope of the claims is commensurate with the scope of the enabling disclosure. Accordingly, Applicants request that the enablement rejection be reconsidered and withdrawn.

Rejections under 35 U.S.C. 112, Second Paragraph

The Examiner rejects claims 1-9, 13, and 14 under 35 U.S.C. § 112, second paragraph, for being vague and indefinite. Specifically:

(a) With respect to claims 1, 2, 4, 6, and 9, the Examiner finds the recitation of "early cancer" to be vague and indefinite; and

(b) With respect to claims 1, 13, 15, and 16, the Examiner finds the recitation of a "one step sandwich enzyme immunoassay" to be vague and indefinite;

(c) With respect to claims 1, 9, and 13, the Examiner finds the recitation of a domain near the N-terminus" to be vague and indefinite; and

(d) With respect to claim 13, the Examiner finds the recitations of "treatment" and "successful therapy and positive prognosis" to be vague and indefinite.

With respect to item (a), the Examiner remains convinced that the term "early cancer" is vague and indefinite, noting that the definition in the specification "does not preclude other stages of cancer or clearly differentiate between a normal person without cancer, who is also symptomless, and a person who is deemed as having early cancer." The Examiner is respectfully reminded that the test for indefiniteness is whether one of ordinary skill in the art would understand the bounds of the claim, when read in light of the specification and in the context of the prior art. Thus, claim language cannot be analyzed in a vacuum but must be interpreted in light of the specification, the teachings of the prior, and the reasonable interpretation given by one of ordinary skill. In this case, "early cancer" is clearly distinct from the "normal" state in that it requires the presence of tumors. Likewise, "early cancer" is clearly distinct from

"advanced cancer" in that the tumors must either be "confined to the site of development (intramucosal) that have not invaded surrounding tissues, or have a "range of invasion [that] is confined to a local area." See p. 4, lines 16-19. Moreover, contrary to the Examiner's suggestion, the term "early" indeed aids in classifying or staging of cancer in that it refers to either "stage 0 (carcinoma in situ) [or] stage I according to the TNM classification", i.e., a cancer stage in which "there are no intravascular invasions or distant metastases, and local tumor ablation alone will lead to complete recovery." See p. 4, lines 24-28. As such, this term "early cancer" as used herein clearly excludes both the normal state as well as advanced stages of cancer that involve intravascular invasions or distant metastases. Accordingly, there is nothing vague, indefinite or unclear about the type of cancer being diagnosed. One of ordinary skill in the art would readily understand the scope of the claim and would clearly be capable of differentiating between a normal person without cancer and a person having early cancer, even though both may be asymptomatic at the time of assessment. Nevertheless, to expedite prosecution, Applicants have amended independent claims 1 and 9 to define early cancer as "cancer at stage 0 or stage I of the TNM classification." Applicants have further attached Appendix 1 to provide an explanation of the TNM classification system, including a description of which parameters are indicative of stage 0 and stage I cancer.

With respect to items (b) and (c), to expedite prosecution, the objectionable terminology has been deleted from the claim, thereby rendering the rejections moot.

With respect to item (d), Applicants have amended the claims to refer to "tumor treatment". Tumor treatment is defined in the specification as including radiation therapy, immunotherapy, chemotherapy, and such, as well as surgical removal. See specification, p. 9, line 5-7. Accordingly, one of ordinary skill in the art, when reading the claims in light of the specification and in the context of the prior art, would readily understand the metes and bounds of the term.

Further regarding item (d), the Examiner indicates that it is unclear what constitutes "successful" therapy and "positive" prognosis. Applicants respectfully submit that these terms are neither vague nor indefinite and that the scope of the instant claims is abundantly clear when

read in context with the specification and the prior art. Not only are these conventional terms of the art having a well-accepted meaning but they are also expressly defined in the instant specification. For example, a cancer treatment is generally deemed a "success" if it results in a return to or progression towards the normal or healthy state. This is reinforced by the instant specification, which states that one can designate a tumor treatment as "successful" if the measured MK value decreases to that of a healthy subject. See p. 9, line 3-5. Likewise, the instant specification states that "[p]rognosis means the response of a patient towards a treatment." See p. 8, lines 35-36. Accordingly, "positive" prognosis refers to a "positive" response to treatment, i.e., movement toward the healthy or normal state. Positive responses to treatment range from an extension of patient life span and a reduction in cancer stage, tumor size or growth rate to partial or complete remission. Thus, one of ordinary skill in the art, when reading the claims in light of the specification and in the context of the prior art, would readily understand the metes and bounds of the claimed terminology.

In sum, Applicants respectfully submit that claims 1-9, 13, and 14 meet the threshold requirements of clarity and precision set forth in35 U.S.C. § 112, second paragraph. Accordingly, Applicants request that the above rejections be reconsidered and withdrawn.

Rejections under 35 U.S.C. 102 & 103

Song et al.:

The Examiner rejects claims 1-8, 13, and 14 under 35 U.S.C. § 102(b) for being anticipated by and under 35 U.S.C. § 103(a) for being obvious in view of Song et al. (Biomedical Research, 1997). According to the Examiner, Song discloses a method for measuring a human midkine protein in the sera of patients with early stage gastric, hepatocellular and lung cancer, wherein detection and measurement of midkine was conducted using an enzyme linked immunoassay using a pair of antibodies.

At the outset, to more specifically describe the present invention and its application, claims 1 and 9 have been amended to reference a method of *screening* for early cancer. As compared to conventional tumor markers, such as CEA, CA 19-9 and AFP, all which are thought

to be quite inadequate for detecting early tumor, the present invention enables a vast screening of individuals to detect potential subjects with early cancer. Thus, the present method constitutes a revolutionary first screening. Although complete physical examinations and subsequent tests would be needed for a definitive diagnosis, the present invention greatly contributes to the eradication of cancer by identifying potentially affected subjects at an early stage when most cancers are treatable.

Furthermore, the present invention, directed to the use of human midkine not simply as a "tumor marker" but specifically as an effective "early tumor marker", is based on the results of measurements from a large number and variety of cancer samples. When using scientific technologies, especially in this field of science (medicine and diagnostics), it is dangerous to draw conclusions from the data of just a few studies. Only once numerous data has been accumulated (and statistically analyzed) can conclusions be drawn for the first time with confidence. In the present invention, the present inventors not only conceived of a way of sensitively dividing cancers into early, moderate and advanced cancers (stages 0 to IV of the TNM classification), but also completed this invention by measuring serum human midkine levels in patients with various types and stages of cancer, and comparing these with healthy patients. In fact, with the exception of the present invention, there are no known functional or secretory proteins that can be measured in body fluids for use as effective indicators for early tumors.

In the instant rejection, the Examiner admits that Song does not explicitly mention "early cancer" or indicate the stage of the cancers assayed. Nevertheless, the Examiner has interpreted the disclosure as reading on early stage cancer because some of Song's samples are denoted as having no metastasis. However, metastasis to the lymph nodes or other organs is an indication of cancer malignancy (or degree). Thus, a cancer that has <u>not</u> metastasized to the lymph nodes is not necessarily an "early cancer", as that term is defined herein (i.e., stage 0 or stage I according to the TNM classification). For example, Stage II liver, pancreatic and colorectal cancers are all defined as having no lymph node or distant organ metastases (i.e., N0, M0). See Appendix 2 attached hereto. However, Stage II cancer is not "early cancer" as that term is defined herein.

Equally, a cancer that has metastasized is not necessarily an "advanced cancer", as that term is conventionally defined (i.e., cancer which has spread from the primary site to other parts of the body, typically M1 or higher). For example, the presence of lymph node metastases are permitted in Stage II testicular, breast and lung cancers. However, such Stage II cancers do not involve distant organ metastases and/or poor prognosis and are thus not typically referred to as "advanced cancer". Accordingly, as there is no direct relationship between a cancer not metastasizing to the lymph nodes and/or distant organs, and that cancer being a stage 0 or I cancer or "early cancer", one skilled in the art cannot reasonably predict the stage of a cancer (i.e., stage 0, I, II, III, etc.) based on the presence or absence of metastases alone.

It appears that the Examiner is suggesting that the detection of early cancer is inherently disclosed by Song et al. However, for a prior art reference to anticipate a claim, the reference must disclose each and every element of the claim with sufficient clarity to prove its existence in the prior art. While anticipation may reside even if the prior art reference relied upon does not expressly disclose minor or well-known aspects of a claimed invention, inherency may not be established by probabilities and possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient. In other words, the missing element or function must necessarily result from the prior art reference. In this case, given the lack of effective early tumor markers at the time of invention and the silence of Song et al. as to the precise stages of the cancers tested, one cannot state with any degree of certainty that the Song reference inherently discloses a method of screening for early cancer as recited in the instant claims. Accordingly, Applicants respectfully submit that the Song reference fails to anticipate the claimed invention.

Regarding method claim 13 *et seq.*, the Examiner suggests that it would have been obvious in view of Song et al. to utilize midkine levels in a comparative analysis of midkine levels to determine the effectiveness of a particular treatment and/or a patient's prognosis. However, in order for serum levels of midkine to correlate to prognosis, there must be a direct relationship between measured midkine levels and a particular diagnosis (e.g., stage of cancer, remission, etc.). In this case, Song et al. expressly admit that they were unable to detect significant correlation between pathological features and serum midkine levels in certain

carcinomas (see p. 377, col. 2). Furthermore, Song et al. fail to disclose or suggest a linear relationship between level of midkine and a particular prognosis or cancer stage. Specifically, degree of differentiation is the most significant survival prognostic indicator of many carcinomas. However, from a review of Song's data in Table 1, it is clear that there is no correlation between degree of differentiation and measured midkine levels. For example, whereas a sample from a patient with poorly differentiated lung carcinoma (case number 52) measured 450 pg/0.5 ml, a sample from a patient with well differentiated lung carcinoma, a patient that is presumably in better condition with a better prognosis, (case number 55) displayed a higher midkine level of 720 pg/0.5 ml. Thus, from the teachings of Song et al., it would not be clear to one skilled in the art that serum midkine levels directly correlate with cancer progression and prognosis. Accordingly, while the Song reference discloses that serum levels of midkine may be "elevated" in certain carcinomas (i.e., greater than 300 pg/0.5 ml) and, therefore, may distinguish the cancerous state from the normal state in such cases, there is no suggestion therein that specific, measured decreases in midkine levels correspond to a progression to a healthy state and/or a positive prognosis. Thus, Applicants respectfully submit that the Song reference fails to render obvious the presently claimed invention.

Ye et al.:

The Examiner rejects claims 1 and 9 under 35 U.S.C. § 102(b) for being anticipated by and claims 1, 9, and 13 under 35 U.S.C. § 103(a) for being obvious in view of Ye et al. (January 1999). According to the Examiner, Ye discloses that there is an association between elevated MK expression and early stage carcinogenesis in humans.

In order to anticipate a claimed invention, a single reference must disclose each and every element of the claim. In this case, while Ye et al. disclose the enhanced expression of midkine mRNA and midkine protein in early stage carcinomas and *tissues*, they do not, however, report enhanced midkine expression in *body fluids*, as recited in the claims as amended. Accordingly, since the Ye reference fails to disclose each and every element of the noted claims, Applicants respectfully submit that it cannot anticipate the present invention.

On the issue of obviousness, the fact that expression of a specific mRNA or protein is enhanced in a tissue or cancer cell line does not necessarily mean that the expression will also be enhanced in body fluids. In fact, it is well known in the art that the production of a variety of substances is enhanced in cancerous tissues and cancerous cell lines, as compared to normal tissues. For example, taking functional or secretory proteins alone, many growth factors such as TGF, EGF and PDGF, proteases such as tissue plasminogen activator, and ectopic proteins such as ACTH (adrenocorticotropic hormone), ADH (antidiuretic hormone), PTH (parathyroid hormone), gonadotropin, prolactin, growth hormone, calcitonin and erythropoietin, are enhanced in cancerous tissues. However, the enhanced expression in cancerous tissues and cancerous cell lines, does not mean that they can be effective "tumor markers" much less "early tumor markers". There is no definite relationship between elevated expression and production of a functional or secretory protein in a cancer tissue, and the incidence of that protein in body fluids (such as blood or urine). Thus, a candidate substance cannot be confirmed to be an effective "tumor marker" without actually measuring the level of that substance in the body fluids of a large number and variety of cancer patients, and then comparing these measured values with those in healthy patients. Accordingly, Applicants respectfully submit that the Ye reference fails to render obvious the presently claimed invention.

Muramatsu et al.:

The Examiner rejects claims 1, 4, 5, 8, and 9 under 35 U.S.C. § 102(b) for being anticipated by and claims 1, 4, 5, 8, 9 and 13 under 35 U.S.C. § 103(a) for being obvious in view by Muramatsu et al. (1996). According to the Examiner, Muramatsu discloses a method of detecting early cancer and assessing midkine gene expression.

As with the Song reference, the Examiner admits that Muramatsu et al. does not explicitly mention "early cancer" or indicate the stage of the cancers assayed. Nevertheless, the Examiner concludes that since the paper does not disclose that the hepatocellular carcinoma assayed was "metastatic or abrogated the liver", the "cancer is regarded as an early cancer, confined to the site of development". However, as noted above and as discussed in the declaration of Dr. Kenji

Kadomatsu submitted herewith, a cancer that has not metastasized to the lymph nodes is not necessarily an "early cancer", as that term is defined herein (i.e., stage 0 or stage I according to the TNM classification). Equally, a cancer that has metastasized is not necessarily an "advanced cancer", as that term is conventionally defined (i.e., cancer which has spread from the primary site to other parts of the body, typically M1 or higher). Accordingly, as there is no direct relationship between a cancer not metastasizing to the lymph nodes and/or distant organs, and that cancer being a stage 0 or I cancer or "early cancer", one skilled in the art cannot reasonably predict the stage of a cancer (i.e., stage 0, I, II, III, etc.) based on the presence or absence of metastases alone.

It appears that the Examiner is suggesting that the detection of early cancer is inherently disclosed by Muramatsu et al. However, as noted above, inherency may not be established by probabilities and possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient to prove its existence in the prior art. In other words, the missing element or function must necessarily result from the prior art reference. In this case, Muramatsu's silence cannot be equated to a single possibility. When reviewing the totality of the disclosure, it is equally reasonable to suggest that the cancers assayed were "advanced cancer", in that they *could* be metastatic. Thus, it is clear that the missing element (i.e., early cancer) does not necessarily flow from the prior art reference. In other words, given the lack of effective early tumor markers at the time of invention and the silence of Muramatsu et al. as to the precise stages of the cancers tested, one cannot state with any degree of certainty that the Muramatsu reference inherently discloses a method of screening for early cancer as recited in the instant claims. Accordingly, Applicants respectfully submit that the Muramatsu reference fails to anticipate the claimed invention.

Applicants further submit that the Muramatu reference does not contain an inherent or enabling disclosure of the presently claimed invention. Specifically, as discussed in Dr. Kenji Kadomatsu's declaration, Muramatsu *et al.* did not classify the experimental samples according to cancer stage because, at the time the experiments described in the reference were conducted, a protein that was secreted into the serum of early cancer patients (i.e., patients categorized at stage

0 or stage I of the TNM classification), and thereby had the potential of becoming a simple and efficient marker for early cancer, was virtually non-existent. Since no one thought that samples derived from early stage cancer patients would yield positive results, no attempt was made to distinguish among cancer stages. In fact, as noted in Dr. Kenji Kadomatsu's declaration, the present inventors' discovery that midkine is indeed found in the serum of early cancer patients and is thereby, an efficient early stage cancer marker that can be simply measured came as a surprise even to the authors of the Muramatsu *et al.* reference. Thus, even though Muramatsu *et al.* teach that midkine levels are increased in the serum of patients with liver cell cancer, it does not necessarily flow that one could predictably use midkine for detecting early cancer because, at the time this reference was published, it was the general view that finding markers for early cancer was virtually impossible.

Since, at the time of publication of the Muramatsu *et al.* reference, it was commonly believed that cancer markers were not present in serum of early cancer patients, those skilled in the prior art would neither have predicted nor expected the positive midkine serum samples to have been derived from patients with early cancer. In fact, only by analyzing a number of samples from patients of various early cancers were the present inventors able to conclusively demonstrate that midkine is indeed an extremely effective marker for screening and detecting early cancer. Thus, it is readily apparent that Applicants' claimed invention of a method of screening for early cancer is neither expressly nor inherently disclosed or suggested by the Muramatsu reference.

Regarding method claim 13 *et seq.*, the Examiner suggests that it would have been obvious in view of Muramatsu et al. to implement a comparative analysis of midkine levels to determine the effectiveness of a particular treatment and/or a patient's prognosis. As noted above with respect to the Song reference, in order for serum levels of midkine to correlate to prognosis, there must be a direct relationship between measured midkine levels and a particular diagnosis (e.g., stage of cancer, remission, etc.). Like the Song reference, Muramatsu et al. simply disclose that serum levels of midkine may be elevated (i.e., greater than 300 pg/0.5 ml) in certain hepatocellular carcinomas. There is no disclosure that serum midkine levels directly

correlate with cancer progression and prognosis nor is there suggestion that specific, measured decreases in midkine levels correspond to a progression to a healthy state and/or a positive prognosis. Thus, Applicants respectfully submit that the Muramatsu reference fails to render obvious the presently claimed invention.

CONCLUSION

Applicants respectfully submit that the claims as amended herein set forth a novel, non-obvious invention. Accordingly, Applicants respectfully submit that claims 1 – 9 and 13 – 16 as amended herein are in condition for allowance and respectfully petition for an early notice of allowance. However, in the event the Examiner feels that further discussion is merited, she is cordially invited to contact the undersigned.

The applicants are also attaching herewith a Supplemental Information Disclosure Statement; form PTO/SB/08, and copies of the cited references.

In view of the foregoing remarks and the amendments set forth above, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

David Saliwanchik

David R. Saliwanchik
Patent Attorney
Registration No. 31,794
Phone: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

DRS/la

Attachments: Request for Continued Prosecution (RCE)
Declaration Under 37 CFR §1.132 of Dr. Kenji
Curriculum Vitae of Dr. Kenji
Appendix 1 and 2

Exhibit 1: Curriculum Vitae of Dr. Kadomatsu Kenji

Name: Kadomatsu Kenji

Date of birth: December 8, 1957

Current Post:

Professor of Molecular Biology,

Department of Biochemistry,

Nagoya University Graduate School of Medicine.

Address: 65 Tsurumaicho, Showa-ku, Nagoya-shi, Aichi Japan 466-8550.

Contact information:

Home Address: 101 Lions Mansion Nakahira,

5-1905 Nakahira, Tenpaku-ku, Nagoya-shi, Aichi Japan 468-0014.

Home phone: 052-804-5283

Office phone: 052-744-2059

Office fax: 052-744-2065

Office email: kkadoma@med.nagoya-u.ac.jp

Education:

April 1976	Entered Kyushu University School of Medicine
March 1982	Graduated Kyushu University School of Medicine
April 1984	Entered Kyushu University Graduate School of Medicine
July 1984-March 1988	Conducted research at the Kagoshima University Faculty of Medicine, Second Department of Biochemistry, Head of Department: Professor Takashi Muramatsu
March 1988	Left school after earning the required credits

Academic title: Doctor of Medicine (Kyushu University; Iken; #830) November 1989

Qualifications: Registered Doctor (Medical Register Number 266038)

Professional Experience:

May 1982	Pediatric Surgeon, Fukuoka City Children's Hospital (Pediatric Surgery)
November 1982	Pediatric Surgeon, Kyushu University Hospital (Pediatrics and Perinatal medicine)
April 1988	Research Associate, Kagoshima University Faculty of Medicine,

	Department of Biochemistry (conducted research into the role of growth factor Midkine, discovered during my time as a graduate student, in ontogenesis)
April 1989	Pediatric Surgeon, Kyushu University Hospital (Pediatric Surgery)
April 1991	Research Associate, Kagoshima University Faculty of Medicine, Department of Biochemistry (conducted functional analysis of growth factor Midkine)
October 1993	Research Associate, Nagoya University School of Medicine, Department of Biochemistry under Professor Takashi Muramatsu (conducted research into the functional expression mechanism of growth factor Midkine, and its application to the diagnosis and therapy of diseases including cancer)
May 1994	Assistant Professor, Nagoya University School of Medicine, Department of Biochemistry
August 1996	Associate Professor, Nagoya University Graduate School of Medicine, Department of Biochemistry
April 2000	Associate Professor, Nagoya University Graduate School of Medicine
September 2004-present	Professor, Nagoya University Graduate School of Medicine

Awards:

1. 1993 Japanese Society of Biochemistry Incentive Award for research into the "Expression and Functional Analysis of Heparin-binding Growth Factor, Midkine"
2. Folkert Belzer Award for Distinguished Research; Removal of alpha-Galactosyl antigens from vascular endothelial cells in pig organs by intravenous infusion of endo-beta-galactosidase C. D. Liu, T. Kobayashi, I. Yokoyama, T. Nagasaka, H. Ogawa, H. Muramatsu, K. Kadomatsu, T. Muramatsu, K. Morozuki, T. Oikawa, Y. Shimano, K. Uchida, H. Takagi, A. Nakao. The 6th Congress of the International Society for Organ Sharing. July 24-27, 2001, Nagoya, Japan。

Affiliations:

Japanese Society of Biochemistry
Japanese Cancer Society
The American Society of Biochemistry and Molecular Biology

Positions: Secretary of the Neuroblastoma Research Society

Other Experience:

October 1990-September 1993	Research Scientist, National Cancer Institute, U.S.A. (Laboratory of Chemoprevention; Head of Laboratory: Dr. Michael B. Sporn)

APPENDIX 1: GENERAL TNM (Tumor-Node-Metastasis) CLASSIFICATION

	T (Tumor)	N (Node)	M (Distant Metastasis)
0	No evidence of primary tumor	No positive lymph nodes	No distant metastases
1	Single tumor contained with primary organ, generally less than 2 cm	Single regional lymph node positive, smaller than 2 cm	Spread to other body organs
2	Single tumor between 2 and 5 cm or multiple tumors	More than one regional lymph node positive or any positive node between 2 and 5 cm	
3	Tumor more than 5 cm or extending into surrounding tissues	At least one node bigger than 5 cm or distant node positive	
4	Tumor of any size with direct spread into adjacent tissue, organs or blood vessels		

APPENDIX 2: CANCER STAGING

Type of Cancer	Stage 0	Stage I	Stage II	Stage III	Stage IV
Liver	Carcinoma in situ	T1; N0; M0	Any T, N0, M0	Any T; N0, N1; M0	Any T; Any N; M1
Pancreatic	Carcinoma in situ	T1, T2; N0; M0	T3; N0; M0	T1-T3; N1; M0:	Any T; Any N; M1
Testicular	Carcinoma in situ	Any T; N0; M0	Any T; Any N; M0 (nodes in abdomen or pelvis)	Any T; Any N; M0 (nodes in chest or above)	Any T; Any N; M1
Colorectal	Carcinoma in situ	T1-2; N0; M0	T3; N0; M0	Any T; N1, N2; M0	Any T; Any N; M1
Breast	Carcinoma in situ	T1; N0; M0	T1-3; N0-1; M0	Any T; Any N; M0	Any T; Any N; M1
Lung	Carcinoma in situ	T1-2; N0; M0	T1-2; N1; M0	Any T; Any N; M0	Any T; Any N; M1